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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/012,904	01/23/1998	HARRY MEADE	G0744.70014US02	2693

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/012,904	MEADE ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21,25-27,29,30 and 36-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21,25-27,29,30 and 36-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Withdrawn Rejections

The rejection of claims 19, 21, 25-27, 29 and 30, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

Two possible construct designs as follows:

A DNA construct for providing a heterologous immunoglobulin (Ig) in the milk of a non-human transgenic mammal comprising a nucleic acid encoding an Ig coding sequence operatively linked to a mammary specific promoter and a 3' non-coding sequence, wherein the construct is produced by inserting the nucleic acid encoding the Ig coding sequence is inserted into a restriction site between the promoter and the 3' non-coding sequence, wherein the Ig coding sequence comprises a nucleic acid encoding an Ig heavy chain coding region and a nucleic acid encoding an Ig light chain coding region, wherein the expression of the nucleic acids result in the concurrent co-expression of an Ig heavy chain protein and Ig light chain protein, wherein the expression of the nucleic acids results in a individual light chain and an individual heavy chain;

A DNA construct composition for providing a heterologous immunoglobulin (Ig) in the milk of a non-human transgenic mammal, comprising a first nucleic acid encoding an Ig heavy chain operably linked to a mammary specific promoter and a 3' non-coding sequence and a second nucleic acid encoding an Ig light chain operably linked to the mammary specific promoter and a 3' non-coding sequence, wherein the mammary specific promoter of the first and second nucleic acid are the same, and wherein the

expression of the nucleic acid results in the co-expression of an independent Ig heavy chain and an independent Ig light chain (see explanation below)

and

A mammary gland epithelial cell comprising the above DNA construct or DNA construct composition, does not reasonably provide enablement for 1) A DNA construct for providing a heterologous Ig in the milk of a non-human mammal that lacks operable linkage between the promoter and the coding sequence for the Ig; and 2) A DNA construct encoding both heavy and light chain Ig genes that comprise two different mammary specific promoters and would not be co-expressed, is withdrawn.

The breadth of the claims was deemed to lack enablement for lacking operably linkage between the promoter and the coding sequence. Applicants amended the claims to include operable linkage language. The breadth of the claims was deemed to lack enablement because the breadth encompasses the use of two different milk-specific promoters, the specification requires concomitant co-expression of the heavy and light chain gene products, and the art suggests two different milk promoter will not predictably result in concomitant co-expression at the appropriate levels. Upon further considerations of the specification, art, and Applicant's arguments, this ground of enablement is withdrawn. While the two different milk promoters may result in different levels of expression of the heave and light chain, adequate co-expression should be achievable and thus is enabling.

The rejection of claims 19, 21, 25-27, 29, and 30, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention, is withdrawn. Applicant amended the claims to remove the indefinite recitations.

The following modifications to the 103 rejection of record are necessitated by the amendments to the claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 21, 25-27, 29, 30, and 36-48, as amended or newly added, are rejected under 35 U.S.C. 103(a) as being unpatentable over Surani (WO 90/04036 pub date:4/19/1990), DeBoer (US Patent 5,633,076 effective filing date 11/27/1990; of record), Meade (US 4,873,316 Patent Date: 10/101989; of record), Bischoff (FEBS

Letters 305:265-268, 1987; of record), Buhler (Bio/Technology 9:835-838, 1991; of record), Gorden et al (Bio/Technology 5:1183-1187, 1987; of record), Ebert (Bio/Technology 8:140-143, 1990; of record), and Stinnakre (FEBS letters 284:19-22, 1991; of record)

Surani teaches a construct for providing an Ig to serum of a transgenic mouse comprising a nucleic acid encoding a human mu heavy chain and a mouse kappa light chain (Example 1, pp. 7-9; and p. 15, lines 1-8). Surani teaches that such constructs can be modified by means known in the art to target the expression of said nucleic acids encoding the heavy chain and light chain to milk of transgenic animals to allow for harvest of the Ig from milk (p. 2, last par, line 1 to p. 3, line 8).

Surani does not teach a promoter that results in the preferential expression of the Ig coding sequence in mammary epithelial cells and milk, a 3' noncoding sequence, and a unique Xho1 restriction site between the promoter and the non-coding sequence wherein the Ig coding sequence is inserted in the Xho1 restriction site.

However, DeBoer teaches an expression construct for introducing a heterologous protein, most preferably a lactoferin (Lf) protein, into the milk of cows, comprising the bovine alpha s1 casein promoter, a 3' non-coding sequence, a Lf coding sequence inserted into a unique restriction site between the promoter and non-coding sequence, and an Xho1 restriction site between the promoter and the 3'coding sequence (col 30, lines 40-50 and Figure 7E and Figure 7F). DeBoer teaches that this expression cassette can be used to express a multitude of heterologous polypeptides including Igs (col 7, lines 4-15). DeBoer teaches that the use of this expression

construct will allow for a high amount of a heterologous polypeptide expression in the milk (col 8, lines 18-23), thus providing motivation to use this expression construct to produce high quantities of a protein, such as light and heavy lg chains. DeBoer does not specifically teach the insertion of the coding sequence for a heterologous polypeptide into the Xho1 site between the promoter and non-coding sequence. However, the Xho1 site is between the necessary regulatory elements and the non-coding sequence. Thus absent evidence to the contrary, it would be within ordinary skill in the art to insert a coding sequence of a heterologous protein into the Xho1 with a reasonable expectation of successful expression of the heterologous protein in the milk of a transgenic mammal. Further, given the finite number of unique restriction sites present between promoter and the non-coding sequence of the expression vector of DeBoer, it would be obvious to an artisan of ordinary skill to choose the Xho1 site with a reasonable expectation of successfully producing a functional expression construct.

Surani does not teach the construct comprising a beta-lactoglobulin promoter, a whey acid protein promoter, or lactalbumin promoter as recited in claim 21.

However, Meade teaches a construct for providing a desired protein in milk of a non-human transgenic mammal comprising a coding sequence for a desired protein to be expressed in milk operatively linked to a milk specific promoter sequence and also encodes a 3' untranslated region (col 1, lines 56-66). Meade further specifies that the milk specific promoter can be any of the casein promoters, beta-lactoglobulin promoter, or any promoter that targets expression to the mammary tissue (col 1, lines 56-60 and col 3, lines 1-15). Meade teaches that this expression system can be used to express

Ig proteins (col 3, lines 31-39). Meade teaches that this expression system also allows for the production of large quantities of the desired protein (col 1, lines 53-55). Bischoff et al. disclose a construct containing a sequence encoding a human α1-antitrypsin variant operatively linked to 17.6 kb of the rabbit whey acid protein promoter, which results in expression and secretion of the a1-antitrypsin variant into milk of a transgenic mouse (see, e.g., page 265, under "DNA construct", page 266, right column, first two paragraphs, and Table 1). Similarly, Gordon et al. disclose a DNA construct containing a sequence encoding human tissue plasminogen activator (t-PA) operatively linked to the promoter an upstream regulatory sequences from the murine whey acid protein gene, which results in expression and secretion of t-PA into milk of a transgenic mouse (se, e.g., pages 1183-1185, under the sections entitled "Construction of t-PA expression vector", and "Expression of biologically active t-PA in milk). In addition, Ebert et al. disclose a DNA construct containing a sequence encoding human tissue plasminogen activator operatively linked to the mouse whey acid protein promoter which results in expression of the protein into goat milk (see, e.g., page 835, right column, under "Generation of transgenic goats", page 836, Figure 1, and page 837, left column, under the section entitled "Expression of tPA in milk"). Moreover, Stinnakre et al. disclose a DNA construct comprising a sequence encoding ovine trophoblast interferon operatively linked to the promoter of the ovine α-lactalbumin gene, wherein the construct is capable of being expressed in the mammary gland of mice and secreted into milk (see, e.g., page 19, right column, under the section entitled "Establishment of the hybrid construct", page 20, under the section "Expression of the transgene", and Figure 1, and page 21,

Table 1). From the teachings of Bischoff et al., Gordon et al., Ebert et al., and Stinnakre et al., one of ordinary skill in the art would have had a high expectation of successfully producing a protein by the mammary gland which is secreted into the milk of a mammal using a DNA construct which contains a whey acid protein promoter or a lactalbumin promoter, which is known in the art to direct the expression of foreign protein in the mammary gland.

The newly added claims specify a DNA construct and a mammary epithelial cell that comprises a first DNA construct encoding the heavy chain operably linked to a milk promoter and a second DNA construct encoding the light chain operably linked to a milk promoter.

From the teaching of Surani it is apparent that the light and the heavy chain protein sequences are independently formed proteins. Therefore, it would have been obvious to an artisan of ordinary skill in the art to predictably make a variant of the DNA construct and mammary epithelial cells comprising two separate expression vectors for the heavy and light chain protein using the methods and teachings of DeBoer and Surani. It would be obvious to an ordinary artisan at the time the inventions was made to predictably produce one expression vector comprising the light chain coding sequence of Surani and the expression cassette of DeBoer and a second expression vector comprising the heavy chain coding sequence of Surani using the same type of expression cassette as is used in the first with a reasonable expectation of success because an artisan of ordinary skill would understand that the light and heavy chain

coding sequence are independent and do not require each other for expression and thus can be present in two separate vectors.

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the present situation, rationales A-E and G are applicable. At the time of the invention, it would have been obvious to an artisan of ordinary skill to introduce the Ig heavy and light chain coding sequences, taught by Surani, into an expression construct

comprising the bovine alpha s1 casein promoter, 3' non-coding sequence, and a unique Xho1 restriction site located between the promoter and non-coding sequence taught by DeBoer using recombinant technologies well established in the art with a reasonable expectation of success. An ordinary artisan would be motivated to introduce the Ig coding sequences of Surani into the expression vector of DeBoer because Surani suggests that these coding sequences can be expressed in the mammary gland to allow for harvest from milk and DeBoer teaches the use of the expression cassette allow for the production of large amounts of a heterologous protein such as Ig proteins. It would have been obvious to an ordinary artisan to choose from a finite number of unique restriction site between the casein promoter and the 3'non-coding sequence to predictably produce an expression construct comprising the Ig coding sequences of Surani inserted into the Xho1 restriction site of the expression construct of DeBoer with a reasonable expectation of arriving at a functional expression vector for introducing heterologous Ig in milk of a transgenic mammal. Further it also would have been obvious to an ordinary artisan to substitute the casein promoter in DeBoer's expression vector with any one of the equivalent milk specific promoters taught in the art, such as a beta-lactogloblin promoter, as taught by Meade, a whey acid Protein promoter, as taught by Bischoff, Gordon, Ebert, or an alpha-lactabumin promoter, as taught by Stinnakre, to predictably obtain the claimed construct using recombinant technologies well established in the art.

Thus, the teachings of the cited prior art in the obviousness rejection above provide the requisite teachings and motivations with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

Response to Arguments

Applicant's arguments filed 12/1/2009 have been fully considered but they are not persuasive. Applicant asserts that one of ordinary skill would not have expected that functional, assembled Ig could be produced with constructs encoding both the heavy and light chains or with cell comprising these DNA constructs. Applicant asserts that an artisan would therefore not have a reasonable expectation of success in producing functional, assembled Ig because the foreign mammary cells would not have been expected to have the co- and post-translational factors uniquely necessary for Ig assembly.

Applicant's arguments are not found persuasive because the claims are not drawn to functional, assembled Ig but rather a DNA construct encoding the heavy and light chain of Igs and mammary cells comprising said DNA construct. It is acknowledged that the intended use the claimed product is to produce Ig, it is not required that the Ig have any particular characteristics are even be fully formed. Therefore, contrary to Applicant's assertion, an artisan would have a reasonable expectation that the DNA construct taught by the combined teachings of the art would be expressed in a mammary cell of a transgenic and even form heterologous Ig structures because the prior art teaches that expression of foreign genes in the

mammary gland, even one that encode complex heterologous proteins, is established in the prior art, as exemplified by De Boer.

The following objection to the claims is necessitated by the amendment to the claims:

Claim Objections

Claims 19, 38, 46 and their dependents are objected to because of the following informalities: Amended claim 19 and newly added claims 38 and 46 recite "wherein the promoter preferentially expresses the heterologous immunoglobulin protein-coding sequence". This recitation is technically inaccurate. Promoters do not “express” coding sequences. Cells, tissues, animal, etc..."express" coding sequences. Promoter, rather" “result in expression", “cause expression”, or “drive expression” or coding sequences in cells. Appropriate correction is required.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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AU 1632

/Thaian N. Ton/
Primary Examiner, Art Unit 1632